IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Keith D. Allen	Examiner:	Qian, Celine X
Serial No.:	09/816,790	Group Art Unit:	1636
Filed:	March 22, 2001	Docket No.:	R855/75658.23500
Title:	Transgenic Mice Containing Sulfotransferase Gene Disruptions		

DECLARATION OF ROBERT DRISCOLL PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Robert Driscoll, residing at 23 Chicory Lane, San Carlos, CA 94070, hereby declare:

1. I am presently employed as Vice President of Intellectual Property & Legal Affairs at Assignee, Deltagen, Inc., in San Carlos, CA. I have also previously served as the Company's Senior Director of Intellectual Property, in which position I managed and oversaw the Company's intellectual property portfolio, including the Company's patent filings. I possess a Ph.D in Chemistry, received from the California Institute of Technology. I also possess a J.D., received from Loyola Law School, Los Angeles. I am a registered patent attorney (Reg. No. 47,536).

2. I am familiar with the above-cited application. I am familiar with the Office Action mailed March 18, 2005. I am aware that the Examiner has rejected the claims, in part, for allegedly failing to meet the utility requirement. I am also aware that the Applicant has argued that a commercial sale of a mouse with a disrupted mSTp1 sulfotransferase allele within the scope of the claimed subject matter ("sulfotransferase gene knockout mouse") should satisfy the utility requirement.

3. In support of the Applicant's aforementioned argument, I hereby state that I have reviewed Deltagen's internal sales records regarding the sulfotransferase gene knockout mouse. According to these records, the sulfotransferase gene knockout mouse has been delivered to at least one (1) large pharmaceutical company. The contractual terms by which the mice were transferred prohibit Deltagen from identifying the name of this company. However, the company is ranked among the top 10 pharmaceutical companies worldwide (based on sales).

4. It is my understanding, based on communications with our pharmaceutical company customers, that transgenic knockout mice obtained from Deltagen are used for studying gene function and for human therapeutic drug development.

5. I further declare that all statements made herein of my own knowledge are true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Robert Driscoll, Ph.D, Reg. No. 47,536

23 June 2005
Date

Industrializing breakthrough discovery

Arthur T Sands
Lexicon Genetics, USA

Predicting drug action using mouse knockouts was pioneered by Lexicon; five years later the full potential of gene knockout technology is beginning to be realized. In combination with comprehensive physiological analysis, the technology delivers novel, *in vivo*-validated targets with the potential for the discovery of breakthrough therapeutics.

Innovation in the pharmaceutical industry depends on breakthrough biological discoveries that reveal new targets for therapeutic intervention. These new targets must provide potent new mechanisms of action to block disease by creating favorable alterations in physiology without undesirable side effects. *In vivo* methods of target validation using gene knockouts have revealed truly rare and valuable targets. This fact stands in direct contrast to the popular myth that the human genome contains thousands of viable drug targets. It seems that a simple truth has been all but forgotten in the pursuit of ultra-high-throughput drug discovery: it is the quality of new targets not the quantity that holds promise for replenishing the pharmaceutical industry's drug discovery pipeline.

There is plenty of evidence that more is not necessarily better. The pharmaceutical industry spends $30 billion each year on research and development - three times more than a decade ago - yet the number of new drugs coming to market has not increased. The industry's product innovation bottleneck is especially critical since $38.6 billion in brand name drugs will be coming off patent over the course of the next three years, creating a market void that drug makers are not prepared to fill.

Physiology must guide discovery

To replenish product pipelines, the industry is looking to biotechnology companies to accelerate the identification and validation of new targets. In order to discover which genes among thousands encode breakthrough targets, industry scientists must conduct rigorous physiological assessments to determine which targets to eliminate and which to pursue. Only those targets that demonstrate the potential to maximize therapeutic effects and minimize side effects should be pursued, thereby reducing the failure rate and increasing the overall efficiency of the drug discovery process.

Since a therapeutic alteration in physiology is the desired endpoint of drug discovery, overly reductionist approaches that ignore the complexity of mammalian physiology are inevitably doomed to failure. Computer modeling, DNA microarrays, proteomics and lower model organisms cannot encompass the complexity of mammalian physiology and may actually distract researchers from a more productive pathway to discovery. Even human genetic studies may be problematic, since they are more likely to reveal genes that cause disease rather than drug targets for future cures.

Just as drugs must act within the context of physiology, novel drug targets must be validated within the context of mammalian physiology before precious resources are expended to develop drugs. Grounding genomics in the discipline of physiology can increase success rates, enhance product pipelines and create safer and superior therapeutics, as well as reduce the enormous amount of time and capital expended for the discovery and development of a drug. Those companies who are equipped to rapidly and effectively integrate physiological information into the target selection process will dominate the next generation of successful drug discoveries.

Of knockout mice and men

After a decade of using mouse knockouts, the data on their predictive power in drug discovery is irrefutable. The top 100 selling drugs in 2001 are directed only to 29 drug targets, many with multiple agents addressing the same target. Of these 29 targets, 23 have been knocked out and in every case the knockout mouse was highly predictive as to the on-target effects and side effects of the associated drugs. These observations lay to rest early theoretical concerns regarding the reliability of the mouse knockout technology to recapitulate actions of drugs in mammalian model systems. The recent near completion of the genomic sequence of mouse and man, now available through either public or private DNA sequence databases, has confirmed the high rate of genomic similarity between the two organisms. Indeed, many decades of research have proved the mouse to be an invaluable tool for the evaluation of biological processes relevant to human disease, including immunology, oncology, neurobiology, cardiovascular biology, obesity and many others. Well-established parallels exist between humans and mice on cellular, biochemical and physiological levels.

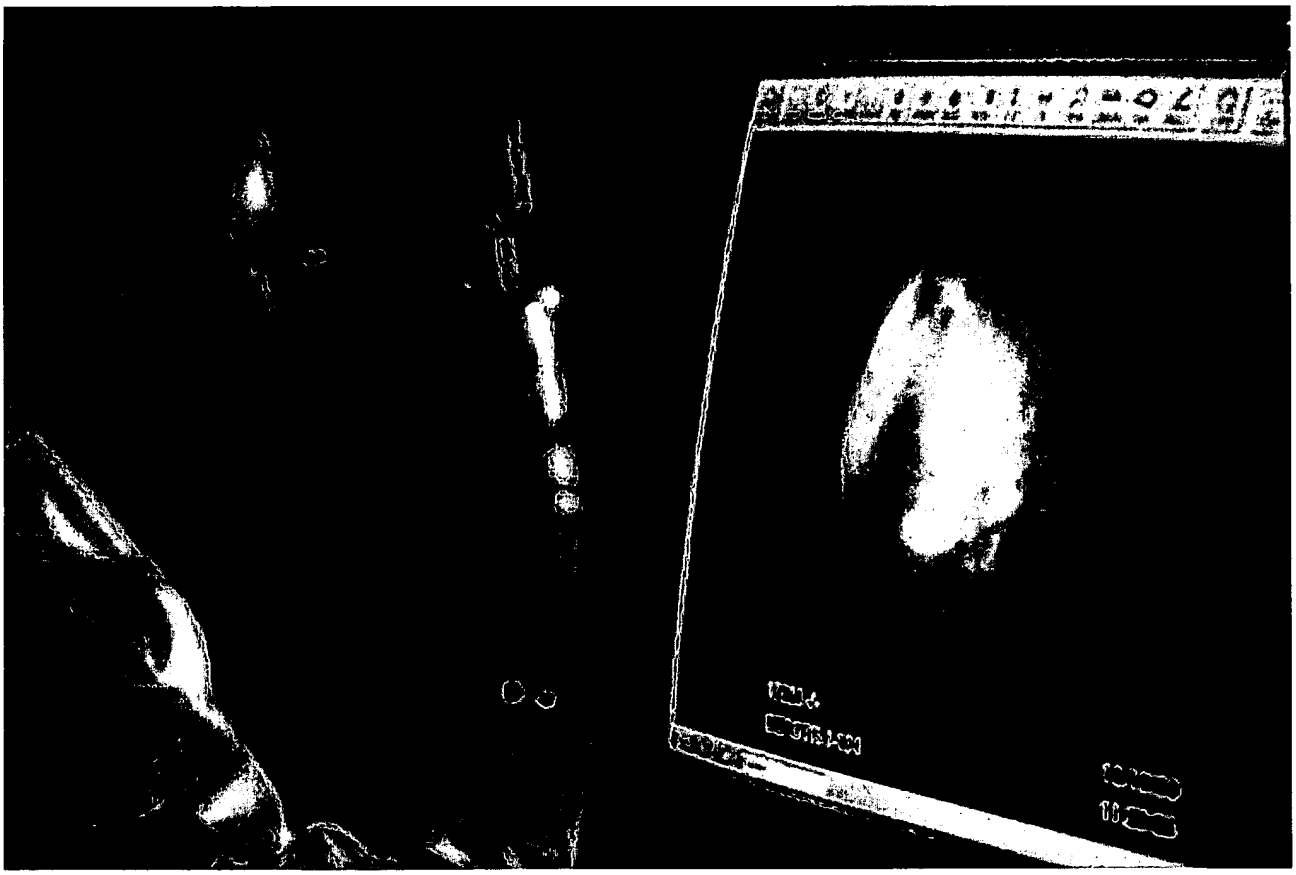
Industrializing discovery

At Lexicon Genetics mouse knockouts are guiding researchers to discover new therapeutic agents which represent the best

physiologic switches in the genome for the treatment of disease. This has required the industrialization of gene targeting, gene trapping and mouse embryonic stem cell technologies, as well as the build-up of significant scientific infrastructure. This infrastructure will allow the company to analyze 5000 genes as mouse knockouts in its Genome5000 program over the next five years. Efforts are concentrated on the unknown function of known gene families for which therapeutic agents can be developed through small molecule chemistry, antibody or therapeutic protein development. These gene families include G protein-coupled receptors, kinases, proteases, ion channels, secreted proteins, transporters and other key enzyme classes. Gene targeting by homologous recombination combined with gene trapping maximizes both selectivity and throughput for large-scale, *in vivo* target validation.

"It seems that a simple truth has been all but forgotten in the pursuit of ultra-high-throughput drug discovery: it is the quality of new targets not the quantity that holds promise for replenishing the pharmaceutical industry's drug discovery pipeline."

The company has deployed a comprehensive, *in vivo* analysis of candidate drug targets that has been modeled after clinical evaluation. Genes analyzed in this way are subject to a superior level of *in vivo* analysis, including physiological function and potential disease indication, providing a robust pipeline of high-value targets. This approach has already proved successful in extracting vital information about the potential medical utility of several new targets in atherosclerosis, diabetes, obesity and CNS disease, among others. Lexicon's physiological analysis utilizes a wide range of the latest medical technologies, including intensive analytical procedures such as the CAT scan for organ system visualization, dual energy X-ray absorptiometry for measurement of percentage fat and lean body mass and bone mineral density, functional magnetic resonance imaging, which allows *in vivo* neurochemical and cardiac analysis, clinical blood and urine chemistries, complete blood cell counts, fluorescent-activated cell sorting, cell-cycle analysis and neurobehavioral testing. Histopathological and gene expression surveys of 55 tissues provide cellular and gene expression data for additional information. Disease challenge models may also be used when indicated to maintain a



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high degree of sensitivity, enabling the detection of subtle phenotypes that may be of significant medical value.

The phenotype derived from the knockout of a specific gene reveals both the potential therapeutic value as well as other target-specific side effects that may be anticipated for a small molecule inhibitor of that target. For instance, a target may display therapeutic potential in inflammation, but might also be critical for renal function. Without a mammalian knockout model, these deleterious target-specific side effects might not be observed until after significant amounts of time and resources have been spent on developing small-molecule compounds and testing them in preclinical or clinical development. When a drug produces a deleterious effect that was not observed in the knockout animal, it suggests that further optimization of the compound's specificity is worthwhile. The ability to produce strong preclinical data to support efficacy and lack of deleterious side effects for a novel target and corresponding lead compound further legitimizes the value of a drug discovery program and provides confidence to move ahead aggressively in development.

> ***"The top 100 selling drugs in 2001 are only directed to some 29 drug targets, many with multiple agents addressing the same target. Of these 29 targets, 23 have been knocked out and in every case the knockout mouse was highly informative as to the on-target effects and side effects of the associated drugs."***

Predicting breakthrough therapeutics

Gene knockouts can be viewed as modeling the biological mechanism of drug action by presaging the activity of highly specific antagonists *in vivo*. This information is critical when making decisions regarding target prioritization for a drug discovery enterprise. Since knockout mice have been shown to model drug activity, they provide an unprecedented level of predictive power over the drug discovery process and can be extremely valuable to the pharmaceutical and biotechnology industries. With the effective use of mouse knockout technology, expensive drug discovery activities such as high-throughput screening, medicinal chemistry, preclinical research and clinical trials can be focused on the drug targets that are most likely to lead to breakthrough therapeutics.

Hypothesis-driven gene targeting and gene trapping place physiology and therapeutic potential at the forefront of the drug discovery process and will provide primary data on the physiological function of virtually all members of 'drugable' gene families over the next few years. However, the full power of knockout mouse technology can only be realized when the predictive nature of knockout mouse phenotypes is applied early in the drug discovery process. The combination of mouse gene knockout technology and comprehensive physiological analysis will provide the pharmaceutical industry with novel, *in vivo*-validated targets with clear potential for the discovery of breakthrough therapeutics.

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FURTHER READING

Firn A, Griffith (2002) **Big pharma hopes to get by with some help from old friends.** *Financial Times* May 01.

(2002) **Worldwide functional genomics market expected to reach $2 billion in 2007.** *PR Newswire: Front Line Strategic Consulting* April 18.

Meeting preview

Sales & Marketing Strategies for Pharma, Europe, 18-20 Sep, Amsterdam
Sales & Marketing for Pharma, USA, 9-11 Oct, Philadelphia, PA, USA

These two conferences, the leading strategic Pharma sales and marketing forums, follow 15 similar high-level eyeforpharma events. Learn how to augment sales and marketing success in the US and Europe through efficient and essential integration of online strategies and professional customer relationship management. Structured to include two days of presentations from leading industry executives and one day of highly interactive workshops, this conference will give you strategic insights to increase campaign success, bolster profits and help maintain a driving competitive advantage.
www.eyeforpharma.com